Remarks/Arguments

Claims 58-62 are presently in the case.

Correction of Inventorship

The request for the deletion of inventors in the application is allegedly deficient under 37 C.F.R.1.48(b) because an oath had not been submitted, a statement of facts by the inventors had not been submitted, the fee had not been paid and it lacked the written consent of the assignee.

Applicant notes that the deletion of inventors was made pursuant to 1.48(b) and not pursuant to 1.48(a). Applicant encloses a copy of the 1.48(b) Amendment as filed. The requirements listed in the Office Action are not the requirements for 1.48(b) amendments.

Rule 1.48(b) states as follows:

If the correct inventors are named in a nonprovisional application and the prosecution of the nonprovisional application results in the amendment or cancellation of claims so that fewer than all of the currently named inventors are the actual inventors of the invention being claimed in the nonprovisional application, an amendment must be filed requesting deletion of the name or names of the person or persons who are not inventors of the invention being claimed. Amendment of the inventorship requires:

(1) A request, signed by a party set forth in 1.33(b) to correct the inventorship that identifies the named inventor or inventors being deleted and acknowledges that the inventor's invention is no longer being claimed in the nonprovisional application; and

(2) The processing fee set forth in 1.17(i).

Applicants note that persons authorized pursuant to 1.33(b) includes registered patent attorneys. Further Applicants note that the Amendment authorized the deduction of any fees. Accordingly, Applicants have met all of the conditions under 37 C.F.R. 1.48(b) and the Patent Office is requested to amend the list of inventors as requested.

Information Disclosure Statement

The Information Disclosure Statement filed 4/12/2005 allegedly fails to comply with the provisions of 37 C.F.R. 1.97, 1.98 and MPEP 609 because the filing is allegedly incomplete. The statement is not accompanied with a listing of the documents on a PTO-1449 form as set forth in 37 C.F.R. 1.98.

Applicants request that the Examiner consider the statement. The Information Disclosure Statement complied with 37 C.F.R. 1.97(c) since it was filed before the mailing date of the final office action and was accompanied by the fee set forth in 1.17(p). There is no requirement for PTO form 1449 for the Examiner to consider the Information Disclosure Statement. Applicants understand that the Examiner is not able to sign off on a Form PTO1449. However, the Examiner is requested to consider the Information Disclosure Statement and indicate that it was considered.

The other Information Disclosure Statement filed 4/12/2005 which included the BLAST results was considered by the Examiner. However, since the BLAST results are allegedly not true publications with a publication date, the Examiner indicated that they would not be printed.

Applicants thank the Examiner for considering the Information Disclosure Statement. Applicants note that each of the BLAST documents was listed separately on PTO Form 1449 with a publication date. The Examiner is requested to reconsider and allow publication of the BLAST results since they comply with the requirement for a publication date.

Claim Rejection - 35 U.S.C. § 101

Claims 58-62 stand rejected under 35 U.S.C. 101 allegedly because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Applicants disagree with the Examiner for the following reasons.

The Examiner states that Applicant has identified a novel neuroligin and that it was clearly known in the art at the time Applicants filed their provisional application that neuroligins were involved in mediating cell-cell recognition between nerve cells, likely at the synapses (page 4 of the Office Action). However, the Examiner states that mere identification that a protein belongs to a family of proteins is not indicative of function nor of utility. The Examiner states that Applicant has not identified a specific disease of condition that the claimed composition is

capable of providing therapeutic properties against. The expectation that the claimed invention can mediate cell-cell recognition between neurons is not sufficient to establish utility.

With regard to the Rat DRG neuronal survival inhibition assay, the Examiner states that there is not sufficient nexus between the *in vitro* data disclosed in the specification and the results to support the treatment of neuropathies. The Examiner admits that the assay has been used to study the effects of various factors on neural development. The Examiner states that a search of the literature fails to reveal a correlation between compositions that tested in the assay and its use as a therapeutic of neuropathic conditions, including neuroblastomas, gliomas, glioblastomas and the like.

Applicants disagree with the Examiner for the following reasons.

Utility Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "**Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility.**" (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for

Examination of Applications for Compliance with the Utility Requirement, set forth in M.P.E.P, 2107 II (B) (1) gives the following instruction to patent examiners: "If the (A)pplicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the Applicant's assertions." (M.P.E.P. 2107 II (B) (1) (ii)). Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

To overcome the presumption of truth based on an assertion of utility by the Applicant, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.** Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Further, the legal standard with respect to *in vitro* or animal model data providing pharmacological activity has been commented on in *Cross v. Iizuka*, 753 F.2nd 1040, 1051, 224 USPQ 739, 747-48 (Fed. Cir. 1985):

> "We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vitro* utility."

Furthermore, M.P.E.P. 2107.03 (III) states that:

> "If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination

thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process."

Thus, the legal standard accepts that *in vitro* or animal model data is acceptable utility as long as the data is "reasonably correlated" to the pharmacological utility described.

Arguments

(1) First, Applicants rely on the identification of the PRO701 protein as a neuroligin based on homology data for patentable utility for the PRO701 protein and antibodies thereto. The Office Action indicates that the invention is not supported by either a specific and substantial or credible asserted utility. Absent any such reasons Applicants maintain that the utility is specific, substantial and credible and request withdrawal of this rejection.

This utility was first disclosed in U.S. Serial 60/080,328 filed April 1, 1998. At page 21, lines 4 - 7 of U.S. Serial 60/080328, Applicants indicate that the PRO701 polypeptide of the invention possesses the biological activity related to that of the neuroligin family.

There are a number of papers which were published prior to Applicants priority document which set forth the function of neuroligins in general. For example, Ichtchenko et al., Cell 81(3):435-443 (1995) (previously provided) discusses neuroligin 1. It indicates that subcellular fractionation of brain demonstrated that neuroligin 1 is enriched in synaptosomes similar to the post synaptic density protein PSD95 (page 438, col. 2). Ichtchenko also teaches that neuroligin 1 copurifies with PSD95 on synaptic plasma membranes. Ichtchenko suggests that the surface expression of neuroligin 1 and β-neurexins on neurons leads to tight interactions between these neurons. Ichtchenko teaches that neuroligin 1's interaction with neurexin contributes to the organization of the synapse, thereby increasing the specificity of the interactions or specifying a defined sequence of interactions. (page 441, col. 2)

Ichtchenko et al., J. Biol. Chem. 271(5): 26776-2682 (1996) (previously provided) teaches two neuroligins, neuroligins 2 and 3, which are similar in structure and sequence to neuroligin 1. All three neuroligins bind to β-neurexins. Ichtchenko indicates that neuroligins mediate cell-cell interactions between neurons.

Nguyen and Sudhof, J. Biol. Chem. 272(41):26032-26039 (1997) (previously provided) discusses that the binding properties of Neuroligin 1 and Neurexin 1 reveal that these molecules

function as heterophilic cell adhesion molecules for mediating cell recognition between neurons. Nguyen and Sudhof also indicate that the esterase-like domain is involved in binding the neurexins. Since the binding properties of neuroligins 2 and 3 are similar to neuroligin 1, they state that the binding of neurexins and neuroligins forms the nucleus for an intercellular junction.

Finally, Irie et al., Science 277:1511-1515 (1997) (cited by Examiner) also indicates that the extracellular domain of neuroligins 1, 2 and 3 tightly bind to the extracellular domain of neurexins. The cytoplasmic domains of all three neuroligins (1, 2, and 3) interact with the amino terminus of PSD-95. They indicate that neuroligins 1, 2 and 3 and neurexins form an intercellular junction between nerve cells. The PSD-95 attach to the cytoplasmic tails of the neuroligins 1, 2 and 3 and recruit NMDA2 receptors and K+ channels to the neuroligin side of the junction.

Clearly it was known in the art at the time Applicants filed their provisional application that neuroligins were involved in mediating the cell-cell recognition between nerve cells at the synapses. Applicants identified a novel neuroligin with these properties.

Nguyen and Sudhof, J. Biol. Chem. 272(41):26032-26039 (1997) indicate that cells expressing neuroligin 1 and neurexin 1 will bind to each other. However, the addition of soluble neurexin lacking an insert inhibited the aggregation of the nerve cells in culture.

One skilled in the art would understand that if the neuroligin function was inhibited or blocked, the synaptic junction would be inhibited or blocked. Thus one skilled in the art would understand that disruption of the neuroligin ability to bind the neurexin would prevent the nerve signals from transmission across the junction. This blockage of nerve signals could be used to treat conditions where transmission of a signal is not desired, such as pain. Clearly the claimed invention had a significant and presently available benefit to the public at the time Applicants filed the provisional application.

After the filing of the provisional patent application, Bolliger et al., *Biochem J.* (2001) 368 581-588 (previously provided) confirmed the structure and function of neuroligin 4 as set forth by Applicants in the provisional application. Bolliger et al., identified that neuroligin 4 binds to the PDZ domains of PSD-95, which is a art recognized characteristic of neuroligins. Accordingly, Applicants' discovery and characterization of PRO701 (now named neuroligin 4 in the literature) was subsequently independently confirmed by other researchers.

Based on Applicants disclosure in Serial No. 60/080,328 and the knowledge in the art at the time of filing, Applicants maintain that the claims are fully enabled. Applicants correctly identified the PRO701 polypeptide as a neuroligin and hence the inherent utility of the PRO701 polypeptide as mediating the cell-cell recognition between nerve cells through a heterophilic junction. Later published works by others have simply recognized and confirmed the sequence and inherent utility of the PRO701 polypeptide previously described by Applicants in their priority document.

The Examiner indicates that the PRO701 sequence is not identical to neuroligin4 , also known as KIAA 1260. Applicants agree that PRO701 and KIAA1260 are not identical, but the polypeptides are so similar as to likely be alleles and/or isoforms of each other. PRO701 has an insert at amino acids 139-158. Applicants note that the location of this insert corresponds to an optional insert found in isoforms of neuroligins 1, 2, and 3. (See Bolliger et al., page 584 where the sequences are compared). The Examiner indicates that the leader sequences differ. Applicants agree that the PRO701 sequence only indicates a leader of 24 amino acids. These 24 amino acids are identical to the last 24 amino acids of the leader indicated by Bolliger. KIA1260 and Bolliger simply have an additional 19 amino acids at the beginning of the leader sequence. The leader sequence is typically removed during processing of the polypeptide in the cell and is not present in the active protein. In addition, PRO701 has one less amino acid at position 456. Applicants believe that PRO701 is an allele or isoform of neuroligin4 and that it is more likely than not that it has the same function and the same utility.

Second, Applicants rely on the " Rat DRG neuronal survival inhibition assay ASSAY #58" for patentable utility for the PRO701 protein and antibodies thereof. This assay first disclosed in PCT/US00/04341 (18 February 2000) and in U.S.S.N. 09/918,585 (30 July 2001) also establishes patentable utility.

The Examiner states that there is allegedly no art-known nexus between the cell growth of neurons in this assay and the predictable treatment of neuropathies and undesirable neural cell proliferation. Further, the ability of the PRO701 protein to inhibit the survival of E14 rat embryo dorsal root ganglia is not a credible use because the cells cultured in this assay are not representative of adult neural cells and tumor cells. It is allegedly well known in the art that sensory neurons undergo programmed cell death during early embryonic development.

(Oppenheim *Annu. Rev. Neurosci* (1991) Vol. 14, pp 453-501) The art allegedly also teaches that factors that cause neonatal cell death, such as peripheral nerve injury, growth factor withdrawal, ionizing radiation, capsaicin do not have the same effect on adult neural cells. Adult neural cells are allegedly more resistant to these factors (Lewis et al., *J. Neuroscience*, Oct. 1999, Vol. 19(20) pp8945-8953). This is allegedly further exemplified by Memberg et al. who teaches that the survival of neural cells depends on specific factors and that the factor dependence changes with the age of the neural cells.

First, Applicants note that the DRG neuronal survival assay is a well recognized and well used assay for measuring compounds which affect the growth of neural cells. The Examiner agrees that the rat DRG neuronal assay has been used in the art to study the effects of various factors on neural development. Applicant note that in vitro sensory ganglia survival and outgrowth assays were used by Levi-Montalcini to identify Nerve Growth Factor. (See excerpt from *Principle of Neural Science,* 4th Ed., Kandel ed. (1991) p1056, previously provided). Secondly Applicants note that both Lewis et al. and Memberg use the DRG survival assay for their analysis. Memberg indicates that proliferation in culture of DRG neuroblasts is consistent with *in vivo* data (page 330, column 1). Clearly this assay is art recognized as being useful to identify compounds with various effects on neural development.

The Examiner has indicated that a copy of Levi-Montalcini was not present in the file. Applicant's note that the Levi-Montalcini disclosure is identified as Kandel et al., Part VIII "The Development of the Nervous System" pp 1056, which reviews the work of Levi-Montalcini. Applicants enclose herewith another copy of this reference.

In Memberg, the comparison was between E12 rat cells and E14.5 rat cells, not between adult and E14.5 rat cells. Memburg indicates that NGF and NT3 act as neurotrophins for E14.5 DRG cells. Memburg does not test whether the neurotrophins which stimulate survival of E14.5 cells are different from those that stimulate survival of adult rat cells. Applicants used E14 rat embryo cells in their assay. This is essentially the same age neurons as Memberg. Memberg does not teach that the use of these neurons is inappropriate.

The Examiner cites Lewis et al. as evidence that adult neural cells are more resistant to peripheral nerve injury. Lewis measured the regulation of HSP27 in DRG of rats by counting the total numbers of HSP27 immunoreactive neurons at postnatal days 2, 7 and 21. Lewis does not

measure the regulation of HSP27 in embryonic DRG cells. One of the assays Lewis uses in making his final determination regarding the effect of HSP27 is the DRG survival assay. Lewis determines that the expression of HSP27 confers a survival advantage to neonatal sensory neurons after injury or NGF deprivation. Clearly Lewis, as do others in the field, agree that the DRG neuronal survival assay is a recognized method of assaying for neurotrophic factors.

The remaining issue is whether there is sufficient nexus between the *in vitro* data disclosed in the specification and the results a skilled artisan would expect in the treatment of neuropathies. "Nexus" requires a factually and legally sufficient connection between the objective evidence provided and the claimed invention, so that the evidence is of probative value in the determination of the issue that it is purported to support. There are peer-reviewed papers in the literature where the authors have used the DRG survival assay to identify neurotrophins and compounds which inhibit neuronal growth. The Examiner admits that the assay has been used to study the effects of various factors on neural development. Finally, this assay or one similar to it was used in the identification of Nerve Growth Factor which is recognized as being a neurotrophin. Positive results with a drug candidate in a recognized *in vitro* assay have long been recognized by the Patent Office and competent courts as sufficient to support utility for claims covering compounds.

As set forth in MPEP 2107 II (B) (1), if the applicant has asserted that the claimed invention is useful for any particular practical purpose and the assertion would be considered credible by a person of ordinary skill in the art, a rejection based on lack of utility should not be imposed. The logic underlying the asserted utility in the present case is not inconsistent with the general knowledge in the art, and would be considered credible by a person skilled in the art.

The Examiner states that Bolliger et al. teaches that the mRNA of the claimed protein has the highest expression in the heart and that neuroligin 4 mRNA was hardly detectable in the brain. With the low incidence of expression in the brain, the Examiner states that it is unclear how the claimed invention could be used for neuropathic conditions.

Applicants note that Bolliger indicates surprise at this result since the cDNA for neuroligin was obtained from brain RNA and indicates that the discrepancy is likely due to different sensitivities of the methods used (Page 587, column 1). Applicants note that Jamain et al., (already provided) detected NLGN4 in male brains. Accordingly, it appears that contrary to

the Examiner's assertion, the gene is expressed in brains. Furthermore, Applicants note that the other tissues tested by Bolliger would contain peripheral nerves. It may be possible that Bolliger is detecting expression of the gene in peripheral nerves. Accordingly, Applicants do not think that this finding of Bolliger negates Applicants asserted utility.

Thus, Applicants believe that they have established patentable utility for PRO701 and its antibodies as instantly claimed and this rejection should be withdrawn.

Claim Rejections - 35 U.S.C. § 112, first paragraph

Claims 58-62 stand rejected under 35 U.S.C. 112, first paragraph. Since the claimed invention is allegedly not supported by either a specific and substantial or credible asserted utility or a well established utility , one skilled in the art would allegedly not know how to use the claimed invention.

Applicants maintain for the reasons set forth in the section on utility that the invention is supported by either a specific and substantial or credible asserted utility or a well established utility. and accordingly, one skilled in the art would know how to use the invention. Withdrawal of this rejection is respectfully requested.

Priority

Applicants note that the subject matter defined in claims 58-62 has been accorded an effective filing date of October 16, 2001 because the instant specification disclosure allegedly fails to meet the requirements of 35 U.S.C. §§ 101 and 112, first paragraph. Accordingly, the claim for priority to any parent application has been denied.

Applicants maintain that the subject matter defined in claims 58-62 is entitled to the priority date of April 1, 1998, the filing date of Provisional Patent Application Serial No. 60/080328. At page 21, lines 4 - 7 of U.S.S.N. 60/080328, Applicants indicate that the PRO701 polypeptide of the invention possesses the biological activity related to that of the neuroligin family. On page 1, lines 9 - 25, Applicants indicate that neuroligins constitute a multi-gene family of brain-specific proteins with distinct isoforms that have overlapping functions in mediating recognition processes between neurons. Moreover, neurexins and neuroligins have

been reported as functioning as adhesion molecules in a Ca^{2+} dependent reaction that is regulated by alternative splicing of beta neurexins. (See also the discussion under utility)

In Serial No. 60/080328, Applicants referenced Ichtchenko et al., *J. Biol. Chem.* 271(5):2676-2682 (1996) and Nguyen and Sudhof, *J. Biol. Chem.* 272(41) 26032-26039 (1997) as references which describe the function of other related neuroligins.

Based on Applicants disclosure in Serial No. 60/080328, Applicants maintain that they are entitled to priority to the filing date of Serial No. 60/080328, i.e. April 1, 1998. Applicants correctly identified the polypeptide and the utility of the PRO 701 polypeptide.

Applicants maintain that the subject matter defined in claims 58-62 is also entitled to the priority date of February 18, 2000, International Patent Application Serial No. PCT/US00/04341. At pages 369-370, Example 140 of PCT Application No. PCT/US00/04341, Applicants indicate that the PRO701 polypeptide of the invention possesses the biological activity related to the inhibition of survival of neural cells in culture. Based on Applicants disclosure in PCT Application No. PCT/US00/04341, Applicants maintain that they are entitled to priority to the filing date of February 18, 2000 for these claims.

35 U.S.C. § 102

Claims 58-62 stand rejected under 35 U.S.C. 102(b) as being anticipated by Ichtchenko et al. (1995). Specifically, Ichtchenko et al. teaches an antibody that binds to a neuroligin protein. Applicants discloses that the protein to which the claimed invention binds has homology to neuroligin proteins. Accordingly, the antibody of Ichtchenko et al. would allegedly bind to the same protein in which the claimed invention binds.

Applicant specifically traverses this rejection for the following reasons.

First of all, Claim 58, and, consequently, those claims dependent from the Claim 58, recite "an antibody that binds specifically to the polypeptide of SEQ ID NO:375." (Emphasis added). Applicants respectfully submit that the term "specific binding" recited in Claim 58 refers to an antibody that binds to a particular antigen without binding to another antigen. Therefore, Claim 58 and the claims dependent from Claim 58, carrying its recitations, clearly refer to an antibody that is able to bind to the PRO701 polypeptide *without* cross reacting with another antigen, including the sequence disclosed in Ichtchenko *et al.* In view of this, the Examiner errs

in assuming that the antibodies claimed in the present application would bind the polypeptide of Ichtchenko. While the amino acid sequence of neuroligin 1 taught by Ichtchenko et al. has some similarity to the PRO701 sequence, there are many different amino acid residues throughout the length of the sequences. For example, the region of residues 620-670 of PRO701 has a different peptide sequence from the peptide sequence of neuroligin 1. One skilled in the art could obtain antibodies which bound to this region of PRO701 and not to neuroligin1. As a result of the requirement of specific binding, the claims pending in this application do not encompass antibodies that bind to the polypeptide of Ichtchenko *et al.*

As the Examiner is well aware, an antibody generally recognizes only a small region on the surface of a large molecule and the structure recognized by an antibody is called an epitope. The structures generally recognized by the antibody are located on the surface of the protein and such sites are likely to be composed of amino acids from different parts of the polypeptide chain that have been brought together by protein folding. Epitopes of this kind are known as conformational or discontinuous epitopes because the structure recognized is composed of segments of the protein that are discontinuous in the amino acid sequence of the antigen but are brought together in the three-dimensional structure. Most antibodies raised against intact, fully folded proteins recognize discontinuous epitopes. Second, the binding sites for the claimed antibodies cannot be simply predicted based on the linear sequence homology between the amino acid sequence of present invention and that of Ichtchenko *et a*l.

The Examiner states that there is no evidence of record that the antibody of Ichtchenko et al., is not an antibody that is encompassed by the claimed invention. Neuroligin 1 has 71.4% identity to neuroligin 4. Thus in the absence of evidence otherwise, the antibody of Ichtchenko et al. would allegedly bind to PRO701.

Applicants note that the claim recites that the antibody specifically binds to PRO701. This means that it does not bind to neuroligin 1. The antibody of Ichtchenko et al. binds to neuroligin 1. Therefore, it cannot be the claimed antibody. Withdrawal of this rejection is respectfully requested.

All claims pending in this application are believed to be in prima facie condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including additional fees for extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2630P1C21. Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: September 28, 2005

Leslie Mooi
Reg. No. 37,047

HELLER EHRMAN WHITE & McAULIFFE LLP
Customer No. 09157/35489
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

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COPY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Le, Emily M.
Avi J. ASHKENAZI, et al.	)	Art Unit: 1648
Application Serial No. 09/978,423	)	Confirmation No: 5291
Filed: October 16, 2001	)	Attorney's Docket No. 39780-2630 P1C21
For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME**	)	**Customer No. 35489**

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DATE MAILED: April 11, 2005

AMENDMENT UNDER 37 C.F.R. §1.48(b)

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

In the above identified application, an Office Action was mailed on January 10, 2005. Having reviewed the application, Applicants have found that as a result of claim amendments made during prosecution, fewer than all of the currently named inventors are the actual inventors of the invention being claimed in the present application. Accordingly, please delete the names of the following inventors, who have not made an inventive contribution to the currently claimed subject matter:

Avi J. Ashkenazi	**Kevin P. Baker**
David Botstein	**Luc Desnoyers**
Dan L. Eaton	**Napoleone Ferrara**
Ellen Filvaroff	**Sherman Fong**
Wei-Qiang Gao	**Hanspeter Gerber**
Mary E. Gerritsen	**J. Christopher Grimaldi**
Kenneth J. Hillan	**Ivar J. Kljavin**
Sophia S. Kuo	**Mary A. Napier**
James Pan	**Nicholas F. Paoni**
Margaret Roy	**Timothy A. Stewart**
Daniel Tumas	**P. Mickey Williams**

Upon entering the present amendment, Audrey Goddard, Paul J. Godowski, Austin Gurney, David Shelton and William I. Wood remain named inventors in this case.

Although no fees are believed to be due at this time, please charge any fees that might become applicable, including any fees for extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39780-2630 P1C21**. Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: April 11, 2005

By: _____
Leslie A. Mooi (Reg. No. 37,047)

HELLER EHRMAN WHITE & McAULIFFE LLP
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

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PRINCIPLES OF NEURAL SCIENCE

Fourth Edition

Edited by

ERIC R. KANDEL

JAMES H. SCHWARTZ

THOMAS M. JESSELL

Center for Neurobiology and Behavior
College of Physicians & Surgeons of Columbia University
and
The Howard Hughes Medical Institute

Art direction by
Sarah Mack and Jane Dodd

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Box 53-1 Discovery of Nerve Growth Factor

Shortly after Viktor Hamburger and Rita Levi-Montalcini determined that target tissues have a critical role in regulating the number of surviving neurons, Elmer Bueker, Hamburger's former student, performed experiments to determine whether the implantation of various tumor tissues into mice might serve as a substitute peripheral target supporting the survival of sensory neurons. Bueker found that mouse sarcoma tissue evoked extensive growth of sensory fibers into the tumor. He also observed that dorsal root ganglia near the site of implanted tumors were significantly larger than the corresponding ganglia on the opposite side of the spinal cord.

These studies were extended by Levi-Montalcini and Hamburger, who noted a dramatic increase in the size of sympathetic ganglia in the vicinity of the sarcoma implant. Further experiments showed that the effect of sarcoma cells was caused by a diffusible factor. Levi-Montalcini developed quantitative assays to measure the effects of the tumor tissue on the survival and outgrowth of axons from sensory and sympathetic ganglia in vitro. Together with Stanley Cohen he began to purify the diffusible molecule, which by this time had been named nerve growth factor (NGF).

In a key biochemical experiment, Cohen and Levi-Montalcini attempted to exclude DNA or RNA as a source of the neurotrophic activity. By chance they used a crude preparation of snake venom as a source of a phosphodiesterase activity intended to degrade any nucleic acids present in partially purified preparations of the factor. Instead they found that the snake venom itself produced a greater degree of axon outgrowth than did NGF itself.

Cohen then investigated a mammalian counterpart of the snake venom gland, the male mouse submaxillary gland, and found that it was a rich source of NGF. This insightful observation provided an abundant source of NGF for purification and protein sequencing. Subsequent work has shown that the protein exists as a complex of three subunits, with a molecular weight of 130,000. The active component is the β subunit, a 118-amino-acid sequence that exists in solution as a homodimer.

turally related to NGF, and the entire family exhibits a distant relationship to members of the transforming growth factor β (TGFβ) family.

The neurotrophins interact with two major classes of receptors. The major signal-transducing receptors are a family of three membrane-spanning tyrosine kinases named trkA, trkB, and trkC, each of which exists as a dimer (see Figure 53-13A). NGF interacts selectively with trkA, whereas brain-derived neurotrophic factor and neurotrophin 4/5 interact primarily with trkB. Neurotrophin 3 activates trkC and, to a lesser extent, trkB. As with other tyrosine kinase receptors, activation of the trk receptors depends on the dimerization of the receptor, a process initiated by the binding of the neurotrophin ligand. Phosphorylation of the cytoplasmic domain of trk receptors recruits specific signaling molecules within the neuron (Figure 53-14), many of which are also used by other tyrosine kinase receptors.

The neurotrophins also bind to a receptor called $p75^{NTR}$ (see Figure 53-13). In contrast to the trk receptors, each neurotrophin binds to $p75^{NTR}$ with similar affinity. The $p75^{NTR}$ receptor is thought to have several functions. First, it can present NGF to trkA. Second, it transmits intracellular signals directly through activation of transduction pathways that depend on signals triggered by membrane lipids. Paradoxically, the activation of the $p75^{NTR}$ receptor in cells that lack trk receptors has been shown to promote rather than prevent neuronal cell death.

In addition to the neurotrophins, other classes of proteins that promote neuronal survival include members of the TGFβ family, the interleukin 6-related cytokines, fibroblast growth factors, and sonic hedgehog. Thus the secreted proteins that have patterning roles at early stages of neural development are also active later in controlling the survival of neurons.

Table 53-1 A Partial List of Neurotrophic Factors

Neurotrophin class
Nerve growth factor
Brain-derived neurotrophic factor
Neurotrophin 3
Neurotrophin 4/5
Interleukin 6 class
Ciliary neurotrophic factor
Leukemia inhibitory factor
Cardiotrophin
Transforming growth factor β class
Transforming growth factor β 3
Bone morphogenetic proteins
Glial-derived neurotrophic factor
Neurturin
Persephin
Artemin
Fibroblast growth factor class
Hepatocyte growth factor

Figure 53
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